

27, and 29, are hereby acknowledged with appreciation. The negative indications with regard to novelty of claims 14-16, 18-19, 28, and 30, and the negative indications with regard to inventive step of claims 1-30, are traversed as follows.

In the paragraphs of the "Citations and Explanations" section of the Written Opinion, claims 14-16, 18-19, 28, and sometimes 30, were asserted to lack novelty over various references including Yamano et al., Le Dall et al., Fujii et al., and Lopes et al. These assertions are clearly in error. The claims involved relate to integrating multiple copies of exogenous DNA into reiterated ribosomal DNA of cells. The methods include not only transforming the cells with a plasmid which is both replicative and integrative, but also repeatedly replicating the cells from the transformation to produce a number of generations of progeny while selecting for cells which include the selection marker, so as to promote the retention of the replicative and integrative plasmid in subsequent generations of the progeny cells and produce progeny cells having multiple integrated copies of the exogenous DNA. None of the references cited teach, suggest, or disclose such a process in which the cells are repeatedly replicated over a number of generations while maintaining the selection pressure. Accordingly, each of the assertions with regard to lack of novelty are incorrect. Withdrawal of the negative indications with regard to the novelty of claims 14-16, 18-19, 28, and 30 is therefore solicited.

In paragraphs 5-10 of the "Citations and Explanations", various sets of claims are asserted to lack inventive step over various combinations of Yamano et al., Le Dall et al., Fujii et al., Lopes et al., Tantirungkij et al., and WO 95/13362 (Purdue Research Foundation). For the following reasons, these assertions should also be reconsidered and withdrawn.

As indicated above as to claims 14-16, 18-19, 28, and 30, the references cited in the novelty rejections fail to teach critical aspects of those claims. Moreover, none of the additional references cited in the inventive step rejections teaches, discloses, or suggests the processes as claimed. Accordingly, it is clear that claims 14-16, 18-19, 28, and 30 possess inventive step over the cited references.

Moreover, the remainder of the claims, which relate to yeasts including multiple integrated copies of XR, XD, and XK, address specific needs in the yeast fermentation industry, in providing highly stable fermentation of biomass including glucose and xylose as primary sugars, without significant loss of fermentive capacity even after numerous generations of culture under non-selective conditions. For example, as directly claimed in claim 25, yeasts in accordance with the invention can substantially retain their capacity for fermenting xylose to ethanol when cultured under non-selective conditions or at least twenty generations. The Examiner's attention is drawn to the specific Examples, for instance Example 7, and FIGS. 4-7, wherein it is clearly demonstrated that yeasts in accordance with the invention (1400 (LNH-ST)) are surprisingly stable, retaining essentially all of their fermentive capacity after twenty generations (see FIG. 7) as compared to corresponding non-stable strains (see FIGS. 4-6). Such surprising stability is nowhere taught, suggested, or disclosed in the cited references. In fact, the cited references themselves teach the unpredictability and potential mitotic instability which occurs in transformed yeast. For example, the article by Lopes et al., in particular at page 472, expressly teaches as to the mitotic instability of its transformed yeasts, and similar teachings are found in other references. Therefore, the present-claimed yeasts which are stable even under non-selective fermentation conditions, and methods for obtaining them, are in fact highly inventive when considered against the teachings of the references.

In light of the above, reconsideration of the negative indications as to inventive step, and the establishment of positive indications as to inventive step for all of claims 1-30, are solicited.

In light of the foregoing, it is submitted that the International Preliminary Examination Report should be positive in all respects.

<p>"Express Mail" label number <u>EMS6589657US</u></p> <p>Date of Deposit <u>22 June 1998</u></p> <p>I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.</p> <p><u>Vigencia Schnupp</u></p> <p>Signature of person mailing paper or fee</p>

Respectfully submitted

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